Recruitment to a Clinical Trial Improves Glycemic Control in Patients With Diabetes

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OBJECTIVE — We assessed the effect upon A1C of recruitment to a clinical trial in patients with diabetes who had been screened and interviewed to determine eligibility but whose therapy was otherwise unchanged.

RESEARCH DESIGN AND METHODS — Eligible trials were selected from the global program of an insulin manufacturer. Included were studies in which patients were seen on a single screening visit, pharmaceutical therapy was not altered before randomization, and A1C was measured in a central laboratory at both screening and randomization. Three trials involving patients with type 1 diabetes ($n = 429$) and three trials involving patients with type 2 diabetes ($n = 611$) were identified for analysis. The main outcome measure was change in A1C. Separate regression equations on the change in A1C were fitted for type 1 and type 2 diabetes and included effects of baseline A1C and the interval between the screening and randomization visits.

RESULTS — A1C changed by −0.13% (range +0.09 to −0.26%) in those with type 1 diabetes at a median of 28 days and by −0.16% (−0.14 to −0.27%) for those with type 2 diabetes at a median of 14 days. The mean change in A1C in those with an interval of ≥28 days was −0.24% for those with type 1 diabetes and −0.23% for those with type 2 diabetes. The reduction was proportional to initial A1C, with large decreases in those with the poorest initial control but no overall change in those at or below the 10th percentile of A1C.

CONCLUSIONS — Recruitment to a clinical trial, independent of any therapeutic intervention, produces improvements in glucose control.

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Diabetes management centers on the patient, who assumes direct responsibility for all aspects of his or her care. This includes day-to-day management of finger-stick glucose measurements, diet, exercise, and glucose-lowering medications (oral tablets and/or insulin injections). Successful integration of these variables is demanding and requires unremitting attention. Behavioral interventions have been shown to improve glucose control (1), but it is not easy to distinguish between the specific benefit of such interventions and the nonspecific effects of study participation, which include increased patient attention and motivation. There is some evidence that patients' glycemic control will benefit simply from participation in a clinical study (2).

We wanted to estimate the influence of study participation on glucose control by retrospective analysis of the effect of the single screening visit that precedes allocation to treatment in a clinical trial. Patients potentially eligible for such trials meet a study representative, usually the study nurse. In the course of this visit, the nature of the study is explained, written consent to participation is obtained, and baseline clinical and laboratory measurements are made. Advice about aspects of management, such as blood glucose monitoring, may also be offered. No other intervention was offered in the trials we considered. Eligibility having been confirmed, the patient is brought back on a second occasion and randomized to new therapy. We set out to analyze the difference in glycemic control, as measured by A1C, between the two visits. Since the analysis was retrospective, the patients and clinical teams participating in these trials were unaware that differences in glucose control might be considered over the period between screening and randomization, thus allowing us to examine the influence of recruitment to a clinical trial upon glycemic control in isolation from any change in therapy.

RESEARCH DESIGN AND METHODS

— Eli Lilly and Company designs and carries out randomized controlled trials of new therapies and/or new regimens for type 1 and type 2 diabetes and therefore has a large database for analysis. Eligible trials were those in which *1*) the only contact before randomization had been a single visit in which the purpose of the study had been explained, informed consent had been obtained, and blood had been taken for testing; *2*) pharmaceutical therapy was unchanged between screening and randomization; and *3*) A1C had been measured at the same laboratory on each occasion.

Of the clinical trials conducted by the sponsor in its global development program for insulin lispro, three trials in patients with type 1 diabetes ($n = 429$) and three trials in patients with type 2 diabetes ($n = 611$), conducted between 1994 and 2001, met the inclusion criteria. The patients in the three trials in type 1 diabetes came from six European countries, and the three trials in type 2 diabetes were conducted in the U.S. Selection criteria for the type 1 diabetic (studies A, B, and C) and type 2 diabetic (studies D, E, and F) study groups differed in that those in the type 1 diabetes studies were in relatively satisfactory glucose control, whereas those in the type 2 diabetes studies were identified on the basis of poor glucose control.

Patients recruited for the trials in type 1 diabetes were aged 18–75 years, had a clinical diagnosis of type 1 diabetes, and all were on four daily injections of human

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*A1C (%) change during the interval between screening and randomization*

Study (reference)	Diabetes type	*n*	Mean at screening	Mean at randomization	Mean ± SD change	Median interval	Predicted mean at median interval	*n* with an interval of ≥28 days	Mean change
A	1	196	7.56	7.33	−0.24 ± 0.72	28	7.44	155	−0.24
B	1	93	7.78	7.52	−0.26 ± 0.67	42	7.54	91	−0.27
C	1	140	7.96	8.05	0.09 ± 0.69)	21	7.81	40	−0.15
	All type 1	429	7.74	7.60	−0.13 ± 0.71	28	7.58	286	−0.24
D	2	130	10.41	10.26	−0.15 ± 0.76	21	10.14	42	−0.12
E	2	117	9.94	9.67	−0.27 ± 0.77	28	9.68	73	−0.29
F	2	364	9.90	9.77	−0.14 ± 0.45	9	9.82	2	*
	All type 2	611	10.02	9.85	−0.16 ± 0.60	14	9.88	115*	−0.23*

*Study F not included since there are only two patients in this category.

insulin. Patients with poor glucose control were excluded; this was defined as an A1C ≥1.5 times the upper limit of the nondiabetic range. Participants in the three trials were subsequently randomized to open or blinded comparisons of insulin lispro (Humalog) with conventional human insulin. The age criteria for trials in type 2 diabetes varied from 40 to 85 years (study D), 25 to 85 years (study E), and 18 to 75 years (study F). All were taking oral glucose-lowering therapy for hyperglycemia and were in suboptimal glucose control. Study D involved patients with sulfonylurea failure, as defined by an A1C >8.5%; study E involved patients with A1C >8.0%, despite treatment with at least one oral glucose-lowering agent; and study F involved patients with A1C ≥8.0%, despite treatment with at least two oral glucose-lowering agents. Subsequent randomization was to combination oral therapy, once-daily NPH insulin plus glyburide, or thrice-daily insulin lispro plus glyburide (study D); to twice- or thrice-daily insulin (study E); and to once-daily NPH insulin plus metformin or a thrice-daily insulin mixture plus metformin (study F). Of six trials included in this analysis, studies A, B, and D have been published in full (3–5), and studies E and F have been published in abstract form (6,7). Free oral medication, but not glucose-monitoring equipment, was offered to patients in the three studies in type 2 diabetes during the run-in period.

Statistical analysis

Data from all six studies were initially combined, irrespective of diabetes type. A linear model was used to explore the effects on change in A1C during the time interval between screening and randomization, A1C at screening, diabetes type, and the interactions between these factors. Regressions were constrained to pass through zero, so that the effects included a linear change over time (interval), an adjustment of this slope for screening A1C (A1C-by-interval interaction), an adjustment of the slope for diabetes type (diabetes type-by-interval interaction), and the three-way interaction. All terms with a P value <0.05 from the type III sums of squares F statistic were included in a hierarchical fashion in the model. As a significant differential slope between diabetes types was found, subsequent analyses were performed separately for type 1 and type 2 diabetes. Sensitivity analyses were conducted by restricting the regression to patients whose interval was at least 28 days. The analyses including all patients produced similar results to these, so the final models used data from all patients. Confirmatory unadjusted means were summarized for each individual study and diabetes type and were compared with the predictions from the fitted models. Data analysis was performed using SAS version 8.2 statistical software (SAS Institute, Cary, NC).

RESULTS — The median interval between screening and randomization ranged from 9 to 42 days in the studies analyzed, with an overall median of 28 days for patients with type 1 diabetes and of 14 days for patients with type 2 diabetes. The mean change in A1C in this interval was −0.13% for type 1 diabetes (range +0.09 to −0.26%) and −0.16% for type 2 diabetes (−0.14 to −0.27%). Among patients with an interval of at least 28 days (median: 31 days for type 1 diabetes, 28 days for type 2 diabetes), mean changes in A1C were −0.24% (type 1 diabetes) and −0.23% (type 2 diabetes) (Table 1).

In both patient populations, the regression equations for change in A1C demonstrated significant effects for the time interval between screening and randomization and the interaction of baseline A1C with this time interval. The following were the final models: A1C change = (−0.0061 baseline + 0.0418) × interval for type 1 diabetes and A1C change = (−0.0074 baseline + 0.0640) × interval for type 2 diabetes. The proportion of variation explained was 11.6% in patients with type 1 diabetes and 11.7% in patients with type 2 diabetes. In both groups, the observed decline in A1C was directly proportional to the screening visit value ($P < 0.001$ for the effect of baseline A1C on the degree of change), such that those with the best initial control showed little response to study recruitment, whereas those with worst control showed the greatest improvement (Figs. 1 and 2). Predictions from the fitted models indicated an overall decline in A1C of 0.16% within 28 days of study recruitment for type 1 diabetes and 0.14% within 14 days for type 2 diabetes (Table 1). The models show that patients with control around the 90th percentile would be expected to improve their control within 45 days by 0.67% (type 1 diabetes) and 1.08% (type 2 diabetes), respectively. The models also show that no change in glycemic control would be expected in those who start around the 10th percentile.

CONCLUSIONS — Many diabetes specialists believe that there are nonspecific benefits of participation in a clinical trial. Possible explanations include more frequent contact with the clinical team,

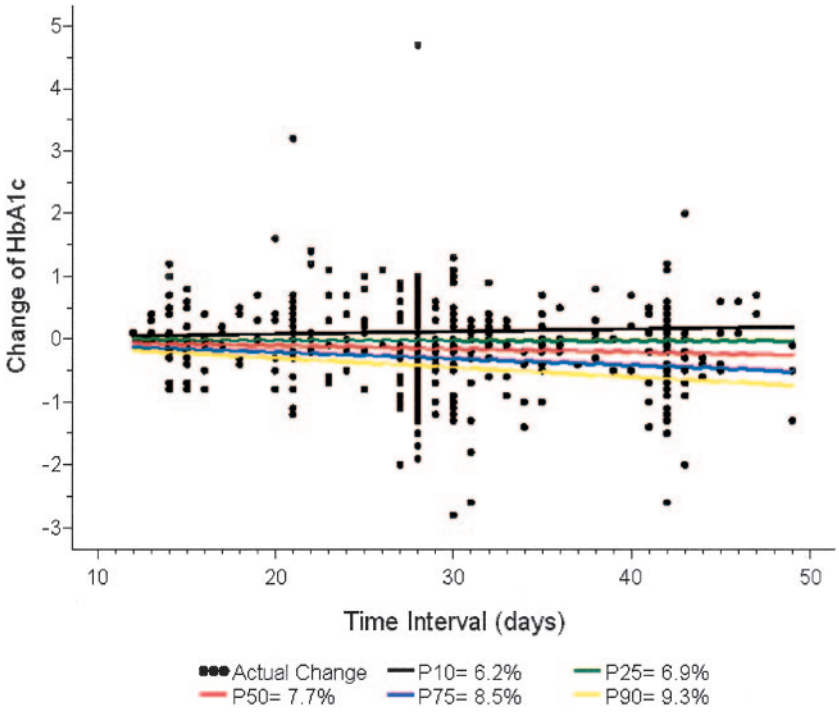

Figure 1—*The change in A1C (%) (black dots) in type 1 diabetic patients* (n = *429) between the screening and randomization visits. The regression lines are derived from the following equation: A1C change = (−0.0061 × baseline A1C value + 0.0418) × duration in days. The change in A1C was inversely related to the value at the screening visit* (P < *0.001). Predicted lines are shown for five percentiles of baseline A1C: 10th percentile (P10), 25th percentile (P25), 50th percentile (P50), 75th percentile (P75), and 90th percentile (P90).*

better information, and increased motivation to do well. We set out to examine the effect of recruitment to a controlled clinical trial upon glycemic control, as judged by changes in A1C between the time of the first visit, in which patients are screened for eligibility, and the subsequent visit, in which those eligible are randomized to therapy. A1C levels reflect mean glycemia over 4–6 weeks but are most strongly influenced by the period immediately preceding the test (8). In our analysis, the typically brief interval between screening and randomization was sufficient to register an effect, although this was not fully expressed in the great majority of patients. Our analysis showed that A1C fell in time-dependent fashion from the time of the screening visit, with an overall observed reduction of just under −0.25% in those waiting ≥28 days for randomization. The fall was proportional to initial A1C, and the observed changes might well be judged of therapeutic relevance when evaluating a new treatment for diabetes.

How can these observations be explained? One possibility is regression to the mean (9), since all patients had elevated A1C at study entry. Patients with type 1 diabetes were, however, selected because of relatively good glucose control, while those with type 2 diabetes were selected for relatively poor control; therefore, one would, on this argument, expect the two groups to change in opposite directions. Hence, regression to the mean cannot fully account for these observations. A second possible explanation relates to the educational content of the screening visit. This typically involves an explanation concerning the nature and purpose of the study, collection of personal data from the patient, brief physical examination, collection of blood and urine samples, and collection of signed consent to participation. Although protocols frequently indicate that patients should be given advice about "optimization of therapy," the time available for this is typically limited in practice. Since no change in pharmaceutical therapy was offered at the time of the screening visit, any subsequent benefit must be attributed to altered patient behavior, whether as a result of specific advice and education given in the course of the screening visit or simply because of increased interest and motivation. The latter appears more plausible.

The classic example of the nonspe-

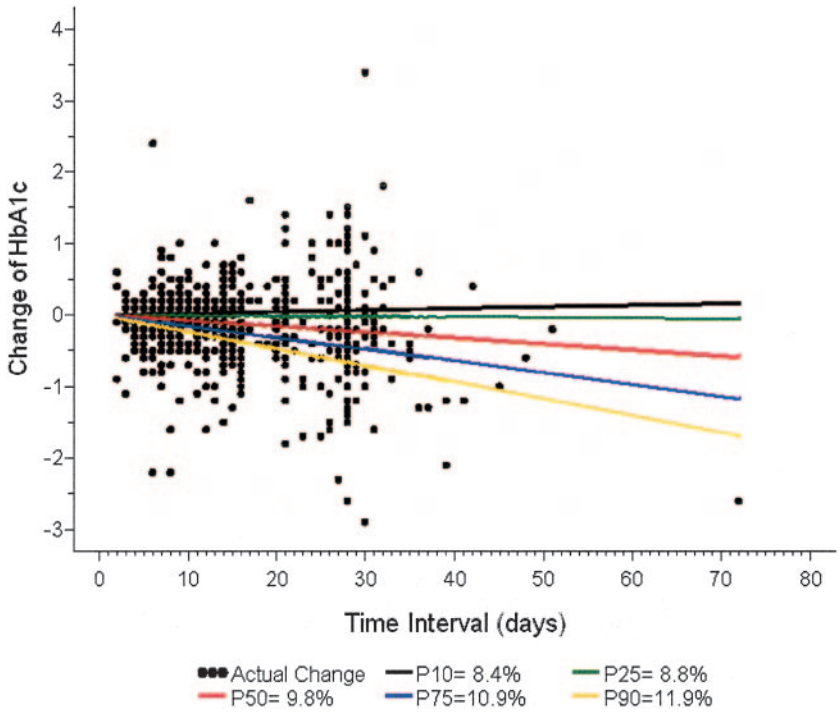

Figure 2—*The change in A1C in type 2 diabetic patients* (n = *611) between the screening and randomization visits. The regression lines are derived from the following equation: A1C change = (−0.0074 × baseline A1C value + 0.0640) × duration in days. The change in A1C was inversely related to the value at the screening visit* (P < *0.001). Predicted lines are shown for five percentiles of baseline A1C: 10th percentile (P10), 25th percentile (P25), 50th percentile (P50), 75th percentile (P75), and 90th percentile (P90).*

cific effect of participation in research derives from a study performed in the Hawthorne plant of the Western Electric Company in Chicago in 1924. Although the original study reports were lost, and the only contemporary record derives from a few paragraphs in a trade journal, this study forms the basis of the frequently cited "Hawthorne effect." This stems from the observation that people alter their behavior when they know that it is being studied in ways that may influence study outcomes. The original study showed that productivity on the factory floor increased in both test and control groups during experiments regardless of whether ambient lighting was adjusted upwards or downwards (10–12). There are several examples of a similar effect in the medical literature. Medical residents in a U.S. hospital participated in a trial of two methods designed to reduce the frequency with which they ordered laboratory tests and X-rays: financial incentive or chart discussion. One-third of the residents acted as control subjects. The chart review group made a 47% reduction, the financial incentive group made a 29% reduction, and the control group made a 36% reduction (13). An example in the area of diabetes relates to measurement of blood glucose by patients. When this technique was introduced, it was assumed that patients who monitor their blood would achieve better control than those who tested their urine. Contrary to expectation, a controlled trial showed that patients randomized to blood or urine tests did equally well when equal time and attention was provided by their health care providers (14).

In conclusion, our study shows that recruitment to a clinical trial involving a single screening visit can produce a clinically useful improvement in glycemic control, especially in those with relatively poor control at study outset. This has implications for the conduct of clinical trials, which should allow for the likelihood that A1C will already be falling in most participants by the time any other intervention is introduced. The conventional baseline measures, recorded at the time of treatment allocation, are therefore not a stable point of reference, and the benefits of any intervention are likely to be overestimated. This underscores the need for controlled comparisons, with a comparable lead-in period and an equal balance of nonspecific interventions. The effect may be of particular importance in the evaluation of washout studies, since the behavioral responses to stopping one medication and starting another may vary in opposite directions; the interval between changes of therapy could also influence the outcome. Clinical trials of patients with diabetes should therefore report A1C at screening, as well as at randomization (to be used as baseline A1C value), and should detail the interval between the two samplings.

Finally, there are implications for patient care. Good clinicians provide variety, novelty, and constant encouragement for their patients, who thus derive nonspecific benefits that may outweigh the advantages of any specific therapy they receive. This may help to explain why there are so many conflicting, yet apparently effective, recipes for improved glycemic control. Voltaire once commented that the main function of doctors was to keep the patient amused "while the disease runs its inevitable course," but this analysis has shown that keeping the patient interested can be a very effective form of therapy.

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